Drinking Water Action Level for Perfluorinated Alkyl Substances (PFAS)

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Abstract

The PFAS compounds perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS) have been the most extensively studied PFAS found in the environment. Spurred by recent detections in drinking water supplies in several states, PFOS and PFOA limits for drinking water have been derived by USEPA (2016), VT (2016), NH (2016), ME (2014), NJ (2007, 2016) and MN (2008). The Connecticut Department of Public Health (DPH) considers USEPA's Health Advisory of 70 ppt for PFOA and PFOS (cap of 70 ppt for PFOA + PFOS) to be health protective and adopts this as our Action Level. As part of the 70 ppt target concentration, DPH includes additional PFAS compounds as follows: perfluorohexanesulfonate (PFHxS), perfluorononanoic acid (PFNA), and perfluoroheptanoic acid (PFHpA). The detected concentration for these PFAS will be added into the PFAS total and this should not exceed 70 ppt in a water sample. The Action Level involves the adoption of an RfD for PFOS and PFOA of 0.02 ug/kg/d as per the USEPA determination, while no RfD is derived at this time for other PFAS. The PFAS compounds have the potential to penetrate the skin. Therefore, the default CT DPH bathing and showering (B/S) advice that pertains to this class of contaminant (no B/S if greater than 3 times the drinking water standard) is applicable to the targeted PFAS compounds.

Introduction

PFOA and PFOS toxicology has been extensively reviewed by USEPA and various states in order to set risk-based drinking water concentrations. There are no federal or state Maximum Contaminant Levels (MCLs) and so these determinations have been set as guidance. The one exception is the draft 2016 New Jersey determination which when finalized would be a state MCL. PFOA and PFOS have very long half-lives in humans and primarily affect the liver, blood lipids, are endocrine disruptive and have adverse effects on in utero development (e.g., growth restriction). As summarized in Table 1, reference doses (RfDs) and drinking water limits have been derived by a number of states and USEPA using standard toxicology approaches. The one exception is that these determinations have involved a rather large pharmacokinetic (PK) adjustment in extrapolating results across species because of the much shorter half-life in rodents compared to humans. The drinking water limits range from 14 parts per trillion (ppt) to 300 ppt although the most recent determinations are in the 14 to 70 ppt range. The differences between these determinations are shown in the table and further described below.

Table 1. Summary of Federal and State PFAS Drinking Water Determinations

Jurisdiction	Chemical	Limit	RfD/Basis	Application to DW
USEPA Health Advisiory, 2016	PFOS, PFOA, combination	70 ppt	PFOA: liver wt effects in rodents across multiple studies → PK adj for HED NOAEL /30 = 0.02 ug/kg/d PFOS: developmental effects in rats; NOAEL→PK adj for HED/30	Water ingestion to pregnant woman: approx 3L/60kg, RSC=20%
VT, 2016	PFOS, PFOA combination	20 ppt	Same as EPA	Water ingestion to 0-1 yr old child, approx. 1.75 liter per 10 kg child; RSC= 20%
NH, 2016	PFOS, PFOA combination	70 ppt	Same as EPA	Same as EPA
NJ, 2016	PFOA	14 ppt	0.002 ug/kg/d based upon BMDL for liver wt effects in adult mice; BMDL extrapolated to HED by PK adjustment, divided by 300x cumulative UF	Water ingestion to adult (2L/70kg), RSC = 20%
Maine, 2014	PFOA	100 ppt	0.006 ug/kg/d; liver wt effects in rodents across 6 studies; BMDL → PK adj for HED /300	Water ingestion to adult, (2 L/70kg), RSC = 0.6 based upon NHANES upper 95th human serum level
Minnesota 2008 HRL[1]	PFOA	300 ppt	0.077 ug/kg/d; liver wt effects in monkeys; BMDL → PK adj for HED / 30	Water ingestion to adult, 3.7 L/day for 70 kg, RSC = 20%
NJ, 2015 Interim GW Criterion	PFNA	13 ppt	$BMDL_{10}$ for liver wt ↑ in mice converted to human serum conc and divided by cumulative UF of 1000x	Water ingestion to serum conc ratio in human adults of 200:1

[1]Health Risk Limit: MN is reviewing their 2008 determination in light of USEPA's 2016 Health Advisory of 70 ppt.

Further Details

Additional perspective on the derivation of drinking water targets for PFOS and PFOA across the jurisdictions listed above is divided into 4 main decision points as follows:

1) Choice of toxicity endpoint: PFOS and PFOA have a wide variety of effects even at relatively low dose with enlargement of liver, endocrine disruption (especially thyroid), and effects on in utero development including developmental neurotoxicity and immunotoxicity all observed at LOAELs or BMDLs in the range of 1 mg/kg/d or below. The endpoints with the greatest data in rodents and monkeys are developmental toxicity and liver enlargement. As seen in the table, RfDs

ranging from 0.002 to 0.077 ug/kg/d have been derived with this difference based upon a number of factors including choice of endpoint, species and study. For example, the highest RfD derived, 0.077 ug/kg/d used the same endpoint (liver weight effects) as in the USEPA determination but the species selected (monkey) required smaller adjustments across species for PK differences than necessitated in the extrapolation from the rat liver weight effects. The in utero developmental endpoints for PFOA were primarily from mouse studies and yielded the same RfD as other endpoints in the USEPA (2016) health advisory derivation. Thus, no one endpoint appears to be the most sensitive or risk driver.

2) Extrapolation of pharmacokinetics from animals to humans: this is based upon fairly straightforward one compartment modeling to go from animal point of departure dose to human equivalent dose (HED) based upon the much longer half life in humans compared to the test animals. This PK adjustment is in the range of 50 to 150 fold depending upon which species is being extrapolated to humans and which PFAS chemicals are involved.
3) Choice of other uncertainty factors to establish RfD: the uncertainty factors have generally followed defaults for cross species (10x) and intra-individual (10x) except that cross species PK was not the typical default but the 3x normally applied for this factor was based upon cross species half life differences. Aside from the PK adjustment a net 30 fold UF was used from a NOAEL or BMDL while in some cases an extra 10 fold was used to account for use of a LOAEL. Also, ME and NJ used larger UFs to account for uncertainties in the PFOA database. These approaches yielded an array of RfDs from 0.002 ug/kg/d to 0.077 ug/kg/d for PFOA and 0.02 to 0.05 ug/kg/d for PFOS. The final choice of RfDs for PFOS and PFOA by USEPA was 0.02 ug/kg/d for both.
4) Application of RfD to drinking water advisory: all derivations shown in the above table except for VT apply the RfD to an adult exposure scenario ranging from the traditional default of 2 L/day for 70 kg body wt to more updated and conservative values, such as USEPA's assumption of 3 L/day for a 60 kg body weight during pregnancy. VT applied the RfD to a 10 kg child ingesting 1.75 L/day given that PFOA and PFOS have developmental toxicity and 1.75 L/day is an upper bound ingestion rate for young children. Aside from the exposure scenario, the Relative Source Contribution (RSC) is a point of difference between ME (RSC = 0.6) vs all others (RSC= 0.2). The higher RSC from ME was based upon comparison to NHANES biomonitoring data for PFOA in which ME used the 95th percentile of the distribution of serum PFOA values to develop the background exposure from diet and other exposures. This serum level from NHANES is 7.5 ug/L while ME showed that the RfD equivalent in drinking water equates to a serum level of 21 ug/L. Thus the background level of exposure uses up only 40% of the RfD leaving 60% that can come from drinking water. This consideration can lead one to a higher drinking water advisory because of the higher RSC, but conversely, it can lead to a greater level of concern given that consumption of water at the drinking water advisory value of 70 ppt leads to a serum level of 7 ug/L which is double the 95th percentile of the background PFOA exposure distribution. Thus, from an exposure perspective, a person ingesting water at USEPA's health advisory for PFOA would theoretically be placed into the upper tail of the exposure distribution. This may not be of public health concern if adverse effects do not start occurring until well above this range. However, as described in a brief synopsis of the epidemiology below, this may not be the case.

NJ's Draft MCL for PFOA, June 2016 (Released August 2016)

The New Jersey Drinking Water Quality Institute (NJDWQI) derived a draft MCL for PFOA of 14 ppt based upon liver weight effects in mice using the BMDL approach to estimate the point of departure. Although this endpoint is different than that used by USEPA, the dose response and point of departure are similar. The reason for the lower target in the draft NJ derivation is an additional 10 fold uncertainty factor for possibly more sensitive endpoints in the PFOA toxicology database, specifically with respect to delayed mammary development in mice, an endocrine disruption endpoint whose PFOA-induced mechanism is not known. In spite of this endpoint being found in mice across 5 publications and in spite of the fact that it has the lowest effect level of any endpoint (0.01 mg/kg/d in Macon et al. 2011), it was not used by USEPA or in the NJ determination for setting the RfD. The lack of precedent for use of this endpoint in regulatory decision-making, the lack of known mechanism and unclear clinical/health implications led to this reluctance. However, the NJ determination added a 10 fold UF for this effect that USEPA did not, which to a large extent explains why the NJ drinking water target is lower than USEPA's. The other consideration by the NJDWQI was that the range of drinking water targets already developed (e.g., 70 ppt, USEPA) or being considered by NJ will theoretically increase the human body burden above what is common at the background level of exposure (e.g., from diet, see above RSC discussion). Given that epidemiology studies suggest that the existing background body burden may be associated with health effects (particularly effects on birth weight), this raises the concern that any increase above background body burden is a public health concern.

CTDPH's review of these considerations is that delayed mammary development is a clearly demonstrated response to PFOA but its dose response is variable across mouse strains with the C57Bl6 and BalbC strains apparently much less sensitive than CD-1 mice (Yang et al. 2009; Macon et al. 2011). Given this and other uncertainties neither USEPA or NJDWQI used this endpoint for standard-setting. The conservatism in applying a 10 fold uncertainty factor for this endpoint combined with also applying a full 20% RSC in spite of the small background contribution to body burden relative to drinking water at the considered concentrations, provides additional conservatism. For example, Maine's derivation as shown in the above table utilizes an additional 10 fold uncertainty factor for possibly more sensitive endpoints (cumulative 300 fold UF) but through a careful analysis sets the RSC at 60%. Had NJ used this larger RSC, the drinking water target would have calculated out to 42 ug/L. The concern raised in the NJDWQI analysis relative to human body burden and effect levels seen in epidemiology studies is addressed to some extent in the synthesis section below.

Synthesis for a Drinking Water Target in CT

The USEPA Health Advisories for PFOS and PFOA of 70 ppt (separately or combined) are risk-based targets that aim to keep exposures from drinking water to a level that is below known effect levels in animals. The RfD of 0.02 ug/kg/d is in full consideration of a range of endpoints and set based upon a toxicokinetic approach and uncertainty factors that are reasonable and consistent with previous EPA assessments. An argument can be made that a database uncertainty factor could have been applied, as

done in ME and NJ, given that in a number of studies a threshold for PFOA effects has not been determined (LOAELS instead of NOAELs), that additional types of vulnerabilities and vulnerable populations could have been assessed, that these compounds are slowly cleared and highly bioaccumulative, that additional endpoints may be affected that need to further assessed (e.g., mammary development, immunotoxicity), and that associations have been reported in epidemiology studes at low levels of exposure within range of US background (Johnson et al. 2014). However, other conservatisms exist in the USEPA derivation such as the water intake rate of 3 L/day for 60 kg body weight and using an RSC of 20% by convention while an RSC of 60% may be more reflective of the underlying exposure and biomonitoring information. The 70 ppt health advisories are within the range of determinations made in other jurisdictions (see above table) and have been thoroughly vetted by USEPA's Office of Water review process as well as external review.

One gap in USEPA's Health Advisory determination is a quantitative analysis of PFOA/PFOS toxicity in humans. This could be a valuable check of the health protectiveness of the advisory drinking water target given that a body of epidemiological evidence has accumulated. Given that 70 ppt can lead to body burdens that are double the 95th percentile of population exposure and that some epidemiology studies have found associations within the range of background exposure (e.g., Johnson et al. 2014, USEPA 2016), it is possible that the health advisory level of exposure is already at a human effect level. The relationship between PFOA and birth weight across 9 epidemiological studies as reported by Johnson et al. 2014 is a decrease of 18.9 grams per ng/ml PFOA in maternal serum. Their meta-analysis of 9 studies was culled from a group of 32 studies in which 10 of the 32 showed a statistically significant association between PFOA and birth weight in humans. If one assumes a normal birth weight of 2500 g (the bottom of the range of normal birth weight), this percent change in birth weight is 0.76% for a 1 ng/ml increase in serum PFOA. The drinking water concentration equivalent to 1 ng/ml (1000 ppt) in serum is 100 fold lower or 10 ppt. Thus, ingestion of PFOA in drinking water concentration at 10 ppt by pregnant women is theoretically associated with a 0.76% decrease in birth weight. Points of departure in RfD derivation based upon the benchmark dose (BMD) approach are typically based off of the 10% effect level, although for reproductive endpoints a BMD can be based upon a 1% or 5% effect level. The drinking water concentrations associated with these possible PODs are: 1%: 13 ppt, 5%: 66 ppt, 10%: 132 ppt. Given that the Johnson et al. (2014) analysis comes from human data for sensitive individuals, additional uncertainty factors may not be needed from these PODs, although a statistical lower bound on the BMD may be feasible and preferable (the BMDL).

The fact that USEPA's animal-based health advisory for PFOA is roughly equivalent to the 5% effect level for decreased birth weight in humans from the subset of studies which are positive for this effect indicates that this drinking water target is in a reasonable risk range. However, we cannot exclude the possibility of a very small effect on birth weight at the 70 ppt Action Level. In other epidemiological findings, effects on blood lipids, impaired immune function, neurodevelopment and endocrine disruption were generally at serum concentrations at or above those described above for birth weight effects (USEPA 2016). Such studies and endpoints may not drive any greater level of risk although they do add to the level of public health concern. Detections below the Action Level may still trigger followup as described in a subsequent section.

Other considerations for PFAS in drinking water are: 1) Additional constituents besides PFOA and PFOS that have been found in drinking water samples; 2) Bathing and showering advice for PFAS in tap water above 70 ppt.

Additional Constituents

A variety of additional perfluorinated alkyl substances (PFAS) are assessed in the standard PFOS/PFOA analytical screen with the following specifically monitored nationwide in the recent Unregulated Contaminant Monitoring Rule (UCMR-3): PFNA (perfluorononanoic acid), PFBS (perfluorobutane sulfonate), PFHxS (perfluorohexane sulfonate) and PFHpA (perfluoroheptanoic acid). The frequency of detection of PFHxS and PFHpA in UCMR-3 testing was similar to that for PFOS and PFOA while the detection of the other two PFASs was much less common. PFHxS and PFHpA are relatively long chain carboxylic acid (PFHpA – 7 fluorines) and sulfonate (PFHxS – 6 fluorines) PFAS compounds with half lives in humans of 8.5 years reported for PFHxS and for PFHpA there are no data in humans but the half-life in rats is relatively short (ATSDR 2015). The half-life for another UCMR PFAS, PFNA is long in rats and so may be on the order of years in humans but data are not available (ATSDR 2015).

In vivo studies in lab animals are less available for these additional PFAS contaminants but there is evidence in rats for effects for PFHxS and PFNA below 1 mg/kg/d in repeat dose studies making the range of potency potentially similar to PFOA and PFOS. The most sensitive endpoint for PFHxS was disorders of the blood (e.g., increased prothrombin time, decreased hemoglobin) while for PFNA it was liver weight changes (ATSDR 2015). Shorter chain PFAS such as PFBS have shorter half-life and may be less toxic. The state of Minnesota has set a drinking water limit for PFBS and PFBA of 7000 ppt at the same time they set a limit of 300 ppt for PFOA and PFOS (MN 2008).

As shown in Table 1, the state of NJ has derived a health-based MCL of 13 ppt for PFNA, which was rounded down to 10 ppt for their interim groundwater guidance. The 2015 support document shows that the rodent and human half life of PFNA is likely to be as long if not longer than PFOA, with several of the toxicology endpoints similar including effects on blood lipids, endocrine effects on thyroid, immune effects, reproductive effects and a consistent increase in liver weight across studies. NJ's BMDL was based upon increased liver weight in mice adjusted for PK differences across species and divided by a cumulative UF of 1000 fold.

A variety of in vitro studies have evaluated the ability of PFOS, PFOA and other PFAS compounds to perturb cell cultures or modulate gene expression through the peroxisome proliferator activation system (PPAR-alpha, gamma). These systems generally show greater activity with longer fluorine chain length, with additive and in some cases synergistic activity between several PFAS compounds and PFOS or PFOA (Wolf et al. 2008, 2014; Hu et al. 2014).

Given the datagaps and uncertainties for PFAS compounds such as PFHxS, PFNA, and PFHpA, the emerging toxicology information, both in vitro and in vivo, suggests that a precautionary approach be taken for these PFAS. Additionally, several have long biological half lives similar to PFOS and PFOA. The

derivation of a recent criterion for PFNA in NJ that is below the USEPA Health Advisory for PFOA/ PFOS highlights the potential activity of these additional long chain PFAS chemicals. Thus, it is a reasonable precaution to add these 3 PFASs to the PFOS and PFOA levels found in a drinking water sample to derive a total that must meet the drinking water health advisory of 70 ppt. Given the shorter half life and derivation of higher drinking water targets for PFBS and PFBA (MN 2008), it is not necessary to add these to the overall total of PFAS compounds in a drinking water sample.

Bathing and Showering Considerations

The CT DPH default guidance for semi-volatile organics as it pertains to PFOA and PFOS is the following:

>30x the drinking water criterion (PFOS/PFOA of 2100 ug/L) – no B/S immediately

3-30x the drinking water criterion (210-2100 ug/L) – no B/S within 3 months

The concern for dermal penetration of PFOS and PFOA is based upon both in vivo and in vitro studies. Blood levels of PFOA were readily detected in dose response fashion following dermal exposure of rats (Kennedy 1985) and mice (Franko et al. 2012). The in vitro penetration of PFOA across mouse and human skin found 40-70% penetration over a 24 hour test (Franko et al. 2012). While this penetration was dependent upon the ionization state of PFOA, it appears that a sufficient percentage is unionized under physiological conditions in the skin to allow the penetration seen in the limited studies available. In other in vitro studies rat skin appeared to be more permeable to PFOA than human skin with the estimated dermal penetration coefficient being 9.49×10^{-7} cm/hour in the isolated human epidermis and 3.25×10^{-5} cm/hour in the isolated rat epidermis (ATSDR 2015). A relatively low dermal dose applied to mouse skin for 4 days (6.25 mg/kg/d) produced a systemic effect, increased liver weight (Fairly et al. 2007). Studies characterizing the dermal penetration or systemic toxicity of dermally applied compound were not found for PFOS or other PFAS.

This evidence of dermal penetration suggests that the CT DPH generic advice regarding bathing and showering limits for semi-volatile organics as described above is reasonable for PFOA and without further information to the contrary, should also be applied to PFOS and other PFAS.

Detection and Feasibility

The proposed DPH Action Level for PFAS is not a detection or feasibility issue as USEPA and other states have already reviewed this for PFOS and PFOA in setting their guidance levels. The other three PFAS included in this determination and summed with PFOS and PFOA (PFHxS, PFNA, PFHpA) are similar to PFOS and PFOA in detection (limits below 70 ppt in recent UCMR-3) and treatment (carbon filtration).

Follow-up for Detections Above and Below the Action Level

Detections above the Action Level of 70 ppt (sum of the 5 PFAS) result in an immediate "do not drink" recommendation which also includes not using the water for food preparation. As discussed above, higher concentrations would trigger a bathing and showering concern. The source of the contamination should be investigated and the individual well can be treated with a carbon filter to address the PFAS contamination.

Detection of PFAS in a drinking water sample is unlikely to be caused by background conditions, and instead may indicate a plume of contamination related to an industrial or firefighting release. Thus, detections of PFAS at any level should be reported to local and state environmental and health authorities (e.g., CT DPH EOHA program, CT DPH Private Well Program, CT DEEP, Local Health Dept.) for possible follow up investigation. Further, well owners with confirmed PFAS contamination, even if below the Action Level, should be made aware of treatment options (carbon filtration) to remove this form of contamination from their drinking water.

References

ATSDR 2015. Draft Toxicological Profile for Perfluoroalkyls. Available at: http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=1117&tid=237

Fairley KJ, et al. 2007. Exposure to the immunosuppressant, perfluorooctanoic acid, enhances the murine IgE and airway hyperreactivity response to ovalbumin. Toxicol Sci. 97: 375-83.

Franko J, et al. 2012. Dermal penetration potential of perfluorooctanoic acid (PFOA) in human and mouse skin. J Toxicol Environ Health A 75(1):50-62.

Hu J et al. 2014. Synergistic effects of perfluoroalkyl acids mixtures with J-shaped concentration-responses on viability of a human liver cell line. Chemosphere 96:81-88.

Johnson PI, et al. 2014. The Navigation Guide - evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. Environ Health Perspect. 122: 1028-1039.

Kennedy GL. 1985. Dermal toxicity of ammonium perfluorooctanoate. Toxicol Appl Pharmacol 81: 348-355.

Macon MB, Villanueva LR, Tatum-Gibbs K, Zehr RD, Strynar MJ, Stanko JP, White SS, Helfant L, Fenton SE. 2011. Prenatal perfluorooctanoic acid exposure in CD-1 mice: low-dose developmental effects and internal dosimetry. Toxicol Sci. 122: 134-145.

Maine 2014. Maximum Exposure Guideline for PFOA in Drinking Water. Available at: https://www1.maine.gov/dhhs/mecdc/environmental-health/eohp/wells/documents/pfoameg.pdf

Minnesota Dept of Health 2008. Health Risk Limits for Perfluorochemicals. Available at: http://www.health.state.mn.us/divs/eh/hazardous/topics/pfcs/finalreport011508.pdf

New Hampshire DHHS 2016. PFCs and Your Health Fact Sheet. Available at: http://www.dhhs.nh.gov/dphs/pfcs/index.htm

New Jersey 2007 Determination Reported as Post et al. 2009. Occurrence and Potential Significance of Perfluorooctanoic Acid (PFOA) Detected in New Jersey Public Drinking Water Systems. Environmental Sci & Technol 43), pp 4547–4554.

New Jersey Drinking Water Quality Institute (2016) Health-Based Maximum Contaminant Level Support Document for PFOA. Available at: http://www.nj.gov/dep/watersupply/pdf/pfoa-hb--mcl-public-review-draftwithappendices.pdf

USEPA 2016. Drinking Water Health Advisories for PFOA and PFOS. Available at: https://www.epa.gov/ground-water-and-drinking-water/drinking-water-health-advisories-pfoa-and-pfos

Vermont DOH 2016. PFOA and PFOS Vermont Drinking Water Health Advisory. Available at: https://anrweb.vt.gov/PubDocs/DEC/PFOA/PFOA%20-%20PFOS%20Health%20Advisories/Vermont/PFOA_PFOS_HealthAdvisory_June_22_2016.pdf

Wolf CJ, et al. 2008. Activation of mouse and human peroxisome proliferator activated receptor alpha by perfluoroalkyl acids of different functional groups and chain lengths. Toxicol Sci 106: 162-171.

Yang, C., Tan, Y.S., Harkema, J.R., Haslam, S.Z. (2009). Differential effects of peripubertal exposure to perfluorooctanoic acid on mammary gland development in C57Bl/6 and Balb/c mouse strains. Reprod. Toxicol. 27: 299-306.